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APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/716,349
	Confirmation Number	7039
	Attorney Docket No.	SEEK-001CON
	Filing Date	November 17, 2003
	First Named Inventor	Ellen L. Berg
	Examiner	Karlheinz Skowronek
	Group Art	1631
	Title: *Function Homology Screening*	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated January 22, 2008. No claims have been allowed. Claims 17 and 19-22 are pending and appealed herein. A Notice of Appeal was filed on May 19, 2008. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. SEEK-001CON to cover the fee required under 37 C.F.R. §1.17(b) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. SEEK-001CON.

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to BioSeek, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

A Notice of Appeal has been filed in the related case, USSN 10/220,999.

STATUS OF CLAIMS

The present application was filed on November 17, 2003, with Claims 1-16. During the course of prosecution, Claims 17-24 were added, Claims 1-16 were canceled, and Claims 18, 23, and 24 were withdrawn by the Examiner as being directed to a non-elected invention. Accordingly, Claims 17 and 19-22 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method for analyzing a candidate compound for a biological activity of interest by using the measurement of multiple parameters in a cell culture assay to produce a biological dataset profile that is indicative of the pathways that are active in the cell culture.

Below is a description of each appealed claim and where support for each can be found in the specification.

Claim 17 claims a method for analyzing a candidate compound for a biological activity of interest, the method including contacting a test mammalian cell culture with the compound, in which the culture includes a plurality of factors in which a plurality of signaling pathways is induced by the

presence of the factors; measuring at least two parameters associated with the plurality of pathways and comparing the measurement of the at least two parameters with the measurement from a control cell culture lacking the compound; and recording the measurements of the test cell culture and the control cell culture to produce a biological dataset profile, in which the biological dataset profile is indicative of the pathways that are active in the cell culture (see specification at page 12, line 7 through page 13, line 24 and page 14, lines 12-30).

Claim 19 claims the method of Claim 17, in which the cells are primary cells (see specification at page 17, line 29 through page 18, lines 10).

Claim 20 claims the method of Claim 17, in which the test cell culture includes at least one activator of a pathway active in the cell culture (see specification at Figures 6 through 9; page 25, lines 1-10; page 30, lines 6-17; page 33, lines 10-22).

Claim 21 claims the method of Claim 17, in which the test cell culture includes at least one inhibitor of a pathway active in the cell culture (see specification at Figures 4 and 5; page 27, line 28 through page 28, line 5; page 32, lines 1-17; page 37, lines 1-6).

Claim 22 claims the method of Claim 17, further including the step of compiling a plurality of the biological dataset profiles in a database (see specification at page 4, line 33 through page 5, line 2; page 16, line 31 through page 17, line 2).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 17 and 19-22 stand rejected under 35 U.S.C. 102(e) as anticipated by Friend *et al.*, U.S. Patent no. 6,801,859 as evidenced by Cole *et al.*, U.S. Patent no. 5,342,777.

II. Claims 17 and 19-22 stand rejected on the ground of nonstatutory obviousness type double patenting as allegedly being unpatentable over claims 1-16 of U.S. Patent No. 6,656,695.

III. Claims 17 and 19-21 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 7, 9, 10, 14, 33, 34, and 35 of copending Application No.10/220,999.

ARGUMENT

I. Claims 17 and 19-22 are not anticipated under 35 U.S.C. § 102(b) by Friend *et al.*, U.S. Patent no. 6,801,859 as evidenced by Cole *et al.*, U.S. Patent no. 5,342,777.

With respect to the rejection under 35 U.S.C. § 102(b), the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 17 and 22, drawn to a method for analyzing a candidate compound for a biological activity of interest, the method including contacting a test mammalian cell culture with the compound, in which the culture includes a plurality of factors in which a plurality of signaling pathways is induced by the presence of the factors, measuring at least two parameters associated with the plurality of pathways and comparing the measurement of the at least two parameters with the measurement from a control cell culture lacking the compound, and recording the measurements of the test cell culture and the control cell culture to produce a biological dataset profile, in which the biological dataset profile is indicative of the pathways that are active in the cell culture, which results may be collected in a database as set forth in Claim 22;

Group II: Claim 19, drawn to the method of Claim 17, in which the cells are primary cells;

Group III: Claim 20, drawn to the method of Claim 17, in which the test cell culture includes at least one activator of a pathway active in the cell culture; and

Group IV: Claim 21, drawn to the method of Claim 17, in which the test cell culture includes at least one inhibitor of a pathway active in the cell culture.

Group I: Claims 17 and 22

The Examiner has rejected the claims of this Group as being anticipated by Friend *et al.*, U.S. Patent no. 6,801,859, as evidenced by Cole *et al.*, U.S. Patent no. 5,342,777. In making this rejection, the Examiner asserts that Friend *et al.* teaches each and every element of the claims with the exception of a plurality of factors that affect a plurality of signaling pathways, which elements the Examiner asserts are shown to be inherent by Cole *et al.*

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

For the reasons detailed below, Appellants submit that the cited references fail to anticipate the claimed invention. Specifically, Appellants submit that Friend *et al.* in view of Cole *et al.* fail to teach, either expressly or inherently, a cell culture including a plurality of factors in which a plurality of signaling pathways is induced by the presence of the factors, as is claimed. The references further fail to teach measuring at least two parameters associated with the plurality of pathways and comparing the measurement of the at least two parameters with the measurement from a control cell culture lacking the compound, as is claimed.

The invention of the present claims, as set forth in independent Claim 17, recites the step of contacting a mammalian cell culture with a compound to be characterized, where the cells in the culture are activated by at least two factors. The cited reference, in contrast, describes methods for screening molecules using cell co-cultures, wherein the cell cultures differ by expression of a single target gene by the over- or under-expression of that target gene. The Friend *et al.* methods do not employ a cell culture comprising at least two factors or in which a plurality of pathways is activated.

The Office Action reiterates that it is inherent to the culture of mammalian cells to include a plurality of factors that affect a plurality of signaling pathways as evidenced by Cole *et al.*, who demonstrate the culture of mammalian liver cells in a culture medium having growth promoting amounts of factors such as epidermal growth factor and retinoic acid. Applicants respectfully submit that it is not inherent to cell cultures to activate a plurality of pathways through multiple factors. It is possible to design a culture where a plurality of pathways is activated. Similarly it is possible to design a culture where a plurality of pathways is not activated.

For example, cells that are cultured continuously in the presence of a factor may down-regulate their receptors, such that over time they no longer respond to the factor, or become refractory. The concentration of factors may be insufficient to induce a plurality of pathways. Cells may also respond in an oscillatory fashion to factors in the culture medium, such that depending on the time point of assessment, the plurality of signaling pathways is not induced. In other cases, the presence of one factor may abrogate the signaling activity of another factor (Sah JF, Eckert RL, Chandraratna RA, Rorke EA. Retinoids suppress epidermal growth factor-associated cell proliferation by inhibiting epidermal growth factor receptor-dependent ERK1/2 activation. J Biol Chem. 2002, 277:9728-35). Applicants respectfully submit that the evidence of Cole *et al.* does not inherently provide Friend *et al.* with each and every element of the present claims, which specify that a plurality of signaling pathways is induced.

In the methods of the present invention, a test agent contacts cells in culture that are stimulated in multiple pathways by the addition of at least two factors. Appellants respectfully submit

that there is no teaching by Friend *et al.* as evidenced by Cole *et al.* that would inform one of skill in the art to perform such analysis in the presence of at least two factors acting on the cell.

Appellants have observed that the activation of cells in multiple pathways reveals properties of test agents that are cryptic in the absence of these factors. Many biologically active agents were found to have no detectable change in parameters when brought into contact with unstimulated cells, as can be found in many cell culture systems. Yet when a biologically active agent is added to cells stimulated in multiple pathways, as in the methods of the invention, distinctive parameter changes could be observed. Accordingly, Appellants submit that "a plurality of factors that affect a plurality of signaling pathways" as set forth in the claimed invention cannot be inherently equivalent to endogenous cell-culture factors, which are asserted to be invariantly present in any cell culture system, because such endogenous factors do not inherently activate a plurality of signaling pathways.

The Examiner has further stated that the addition of factors simultaneously with the agent is not recited in the rejected claims. Appellants submit that the instant claims positively recite that the "biological dataset profile is indicative of the pathways that are active in said cell culture." Upon reading the claims in light of the specification, as the law requires, it is clear to the ordinarily skilled artisan that the claimed "factors" must be as described in the specification, i.e. specific factors added to stimulate signaling pathways, and not simply endogenous factors which are always present in any cell culture, as the Examiner asserts is taught by Cole *et al.* In contrast, the factors contemplated by the methods of the instant claims are modulatory of specific pathways in order for the dataset profile to be informative, as required by the claim.

The Patent Office asserts that Friend *et al.* teaches the use of mammalian cell cultures, at column 44, line 39-40 and column 10 lines 56-59, in the context of cell systems having perturbed biochemical pathways. Appellants respectfully submit that the citations fail to teach the methods of the present invention.

Col. 10, lines 56-59 of Friend *et al.* reads as follows:

In most preferred embodiments of the invention, the cells used for cluster analysis are of the same type and from the same species as the species of interest. For example, human kidney cells are preferably tested to identify consensus profiles to evaluate drugs or therapies that are used to treat disorders involving human kidney cells. However, in some preferred embodiments, the biological samples are not of the same type or are not from the same species as the species of interest. For example, in certain preferred embodiments, yeast cells may be used to define consensus profiles that are useful, e.g., in comparing or evaluating drugs or drug candidates used or intended for human therapies.

Col. 44, lines 39-40 of Friend *et al.* reads as follows:

For each of the mammalian expression systems described above, as is widely known to those of skill in the art, the gene of interest is put under the control of the controllable promoter, and a plasmid harboring this construct along with an antibiotic resistance gene is transfected into cultured mammalian cells. In general, the plasmid DNA integrates into the genome, and drug resistant colonies are selected and screened for appropriate expression of the regulated gene. Alternatively, the regulated gene can be inserted into an episomal plasmid such as pCEP4 (Invitrogen, Inc.), which contains components of the Epstein-Barr virus necessary for plasmid replication.

Appellants respectfully submit that the cited sections of Friend *et al.* do not teach a method of analysis wherein an agent is contacted with a mammalian cell culture, wherein said culture comprises a plurality of factors and wherein a plurality of pathways is induced by the factors. The cited paragraph from column 10 suggests that screening drugs for treatment of kidney cancer might use kidney cancer cells, but that in preferred embodiments, yeast cells are used. The cited paragraph from column 44 teaches a gene of interest may be expressed on a vector. It is not seen how these sections could be interpreted as teaching cell cultures in which a plurality of factors is used to activate a plurality of signaling pathways.

Appellants respectfully submit that the cited art fails to teach each and every element set forth in Claims 17 and 22, either expressly or inherently described, in a single prior art reference. Reversal of the rejection is requested.

Group II: Claim 19

The Examiner has rejected the claim of this Group as being anticipated by Friend *et al.* as evidenced by Cole *et al.* Claim 17 is as described above. Claim 19 depends from Claim 17 and is drawn to the method of Claim 17 in which the cells are primary cells.

With regard to the rejection of the claims in this Group, Appellants submit that Friend *et al.* nowhere teaches primary cells and, in every case, instead teaches the use of cell *lines*, including yeast cell lines, in carrying out its methods. One of skill in the art understands that a primary cell is not a cell line. Cells that are cultured directly from a subject are known as *primary cells*. Primary cell cultures typically have a limited lifespan, and can be sensitive to factors and agents that do not affect established cell lines. After a certain number of population doublings cells undergo the process of senescence and stop dividing. An established or immortalised *cell line* has acquired the ability, either through random mutation or deliberate modification, to proliferate indefinitely. There are numerous well established cell lines representative of particular cell types.

Appellants note column 45, section 5.5.2 of Friend *et al.*, by way of example, which recommends the use of the Jurkat T *cell line* as a model cell on which to conduct transfection or transduction techniques in order to generate cell lines with controllable perturbed expression for studying immunosuppressive drug candidate effects. Friend *et al.* states:

> A particular example of the use of this method is the search for drugs that target the src-family protein tyrosine kinase, lck, a key component of the T cell receptor activation pathway (Anderson *et al.*, 1994, Adv. Immunol. 56:171-178). Inhibitors of this enzyme are of interest as potential immunosuppressive drugs (Hanke J H, 1996, J. Biol Chem 271(2):695-701). A specific mutant of the Jurkat T cell line (JcaM1) is available that does not express lck kinase (Straus *et al.*, 1992, Cell 70:585-593). Therefore, introduction of the lck gene into JCaM 1 by transfection or transduction permits specific perturbation of pathways of T cell activation regulated by the lck kinase. The efficiency of transfection or transduction, and thus the level of perturbation, is dose related. The method is generally useful for providing perturbations of gene expression or protein abundances in cells not normally expressing the genes to be perturbed.

Thus, where Friend *et al.* identifies as a goal the study of T cell activation, Friend *et al.* suggests the use of Jurkat T cells, an immortalized T cell **line**, instead of primary cells. Further, Friend *et al.* teaches the use of yeast cells to study the effects of drug candidates (see Sections 5.3.1, 5.3.5 and the reference generally). The Cole *et al.* reference teaches only liver epithelial cell **lines**. Accordingly, the cited references provide no guidance to the ordinarily skilled artisan to use of primary cells for studying the mechanism of agents on cell pathways; indeed, the references teach to the contrary.

Appellants respectfully submit that the cited art fails to teach each and every element set forth in Claim 19, either expressly or inherently described, in a single prior art reference. Withdrawal of the rejection is requested.

Group III: Claim 20

The Examiner has rejected the claim of this Group as being anticipated by Friend *et al.* as evidenced by Cole *et al.* Claim 20 depends from Claim 17 and is drawn to the method of Claim 17 in which the test cell culture includes at least one activator of a pathway active in the cell culture. Appellants submit that Friend *et al.* as evidenced by Cole *et al.* fails to anticipate the claimed invention.

As cited above, the purpose of the Friend *et al.* methods, as described in the Invention Summary, is:

> for determining a "consensus" profile for a biological response, such as the response of an organism to a group or family of drugs and/or drug candidates. The consensus profile obtained by the methods of this invention represents an ideal, desired activity profile across some standard measurement set such as the cellular constituents of a cell or model organism, or of an organism destined for treatment, e.g., by drug therapy. As such, the consensus profiles of this invention indicate those elements or patterns in a biological profile which the individual compounds have in common. Preferably, such elements or patterns are associated with a particular biological effect--most preferably a particular, desired, therapeutic effect, or "ideal" effect. Accordingly, the present invention also provides methods for obtaining a response profile for a particular compound, such as for a particular drug or drug candidate, and for comparing the response profile of the particular compound to the consensus profile to determine the extent to which the particular compound exhibits a particular, i.e., "ideal," effect as opposed to "non-ideal" or toxic effects.

This passage makes clear that Friend *et al.* does not teach the use of at least one activator of a pathway active in a cell culture. Friend *et al.* methods employ measurements that simply define sets of co-regulated cellular constituents, and define common response motifs among the sets in response to a test drug. The methods of Friend *et al.* require these steps, because the reference is directed to deriving a consensus profile from a desired or "ideal" agent (sifting through all of the transcripts to find a set that reproducibly co-regulates).

Put simply, whereas Friend *et al.* collects gene expression data by exposing cells to a given drug and determining clusters of genes which covary in response to that drug, the present methods instead contacts an agent with cells in culture that are stimulated in multiple pathways by the addition of at least two factors. Appellants respectfully submit that there is no teaching by Friend *et*

al. in combination with Cole *et al.* that would inform one of skill in the art to perform such analysis in the presence of at least two factors acting on the cell, whether the factors are activators or suppressors.

Appellants respectfully submit that the cited art fails to teach each and every element set forth in Claim 20, either expressly or inherently described, in a single prior art reference. Withdrawal of the rejection is requested.

Group IV: Claim 21

The Examiner has rejected the claim of this Group as being anticipated by Friend *et al.* as evidenced by Cole *et al.* Claim 21 depends from Claim 17 and is drawn to the method of Claim 17 in which the test cell culture includes at least one inhibitor of a pathway active in the cell culture. Appellants submit that Friend *et al.* as evidenced by Cole *et al.* fails to anticipate the claimed invention.

As cited above, the purpose of Friend *et al.* methods as described in the Invention Summary is:

> for determining a "consensus" profile for a biological response, such as the response of an organism to a group or family of drugs and/or drug candidates. The consensus profile obtained by the methods of this invention represents an ideal, desired activity profile across some standard measurement set such as the cellular constituents of a cell or model organism, or of an organism destined for treatment, e.g., by drug therapy. As such, the consensus profiles of this invention indicate those elements or patterns in a biological profile which the individual compounds have in common. Preferably, such elements or patterns are associated with a particular biological effect--most preferably a particular, desired, therapeutic effect, or "ideal" effect. Accordingly, the present invention also provides methods for obtaining a response profile for a particular compound, such as for a particular drug or drug candidate, and for comparing the response profile of the particular compound to the consensus profile to determine the extent to which the particular compound exhibits a particular, i.e., "ideal," effect as opposed to "non-ideal" or toxic effects.

This passage makes clear that Friend *et al.* does not teach the use of at least one inhibitor of a pathway active in a cell culture. The methods of Friend *et al.* employ measurements simply to define sets of co-regulated cellular constituents, and to define common response motifs among the sets in response to a test drug. The methods of Friend *et al.* require these steps, because the reference is directed to deriving a consensus profile from a desired or "ideal" agent (sifting through all of the transcripts to find a set that reproducibly co-regulates).

Put simply, whereas Friend *et al.* collects gene expression data by exposing cells to a given drug and determining clusters of genes which covary in response to that drug. In contrast, Appellants' methods employ a step in which a test agent is contacted with cells in culture that are stimulated in multiple pathways by the addition of at least two other factors. Appellants respectfully submit that there is no teaching by Friend *et al.* in combination with Cole *et al.* that would inform one of skill in the art to perform such analysis in the presence of at least two factors acting on the cell, whether the factors are activators or suppressors, such that the resulting dataset is indicative of the pathways that are active in the culture.

Appellants respectfully submit that the cited art fails to teach each and every element set forth in Claim 21, either expressly or inherently described, in a single prior art reference. Withdrawal of the rejection is requested.

In view of the discussion above, the Appellants submit that Friend *et al.* as evidenced by Cole *et al.* fails to anticipate the claims of any of Groups I through IV and respectfully request reversal of this rejection.

II. The rejection of Claims 17 and 19-22 on the grounds of nonstatutory obviousness type double patenting as allegedly being unpatentable over claims 1-16 of U.S. Patent No. 6,656,695 should be reversed in view of the enclosed terminal disclaimer.

Claims 17 and 19-22 have been rejected under the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-16 of U.S. Patent no. 6,656,695. Appellants have enclosed herewith a terminal disclaimer. Reversal of the rejection is requested.

III. The provisional rejection of Claims 17 and 19-21 on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 7, 9, 10, 14, 33, 34, and 35 of copending Application No.10/220,999 should be converted to a double-patenting rejection upon issue.

Appellants have enclosed herewith a terminal disclaimer. Reversal of the rejection is requested.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 17 and 19-22 under 35 U.S.C. § 102(b) and the rejection of Claims 17 and 19-22 on the grounds of nonstatutory obviousness type double patenting be reversed; that the provisionally rejected Claims 17 and 19-21 be permitted to issue; and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: July 7, 2008

By: _____
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CLAIMS APPENDIX

17. (previously presented) A method for analyzing a candidate compound for a biological activity of interest, the method including:

contacting a test mammalian cell culture with the compound, wherein the culture includes a plurality of factors wherein a plurality of signaling pathways are induced by the presence of the factors;

measuring at least two parameters associated with the plurality of pathways and comparing the measurement of the at least two parameters with the measurement from a control cell culture lacking the compound, and

recording the measurements of the test cell culture and the control cell culture to produce a biological dataset profile, wherein the biological dataset profile is indicative of the pathways that are active in the cell culture.

19. (previously presented) The method of Claim 17, wherein the cells are primary cells.

20. (previously presented) The method of Claim 17, wherein the test cell culture includes at least one activator of a pathway active in the cell culture.

21. (previously presented) The method of Claim 17, wherein the test cell culture includes at least one inhibitor of a pathway active in the cell culture.

22. (previously presented) The method of Claim 17, further including the step of compiling a plurality of the biological dataset profiles in a database.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.